Statistical Analysis of Cost-effectiveness Data From Clinical Trials

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Model Definitions

Consider the cost-effectiveness comparison between a new health care intervention, referred to as *Treatment* (denoted *T*), with current practice, referred to as *Standard* (denoted *S*)

Treatment (*T*)
versus
Standard (*S*)

Model Definitions

We need to estimate

Δ_e, the difference in mean effectiveness $(= e_T - e_S)$

- survival (1,0): Δ_e = prob.(survival)$_T$ – prob.(survival)$_S$
- survival time: Δ_e = mean survival time$_T$ – mean survival time$_S$
- quality-adjusted survival time:

  Δ_e = mean q-a survival time$_T$ – mean q-a survival time$_S$

Δ_c, the difference in mean cost $(= c_T - c_S)$

Also need estimates of $V(\hat{\Delta}_e)$, $V(\hat{\Delta}_c)$ and $C(\hat{\Delta}_e, \hat{\Delta}_c)$

Model Definitions

Let λ be the threshold value for a unit of effectiveness

- survival (1,0): λ = threshold value to save a life
- survival time: λ = threshold value for a year of life
- quality-adjusted survival time:

  λ = threshold value for a quality-adjusted life year (QALY)

Define incremental net benefit (INB) as:

$$b(\lambda) \equiv \lambda\Delta_e - \Delta_c$$

"incremental" because it is difference between T and S and it is "net" of costs

INB $= \lambda\Delta_e - \Delta_c = \lambda(e_T - e_S) - (c_T - c_S) = \lambda e_T - c_T - (\lambda e_S - c_S)$ = NB$_T$ – NB$_S$

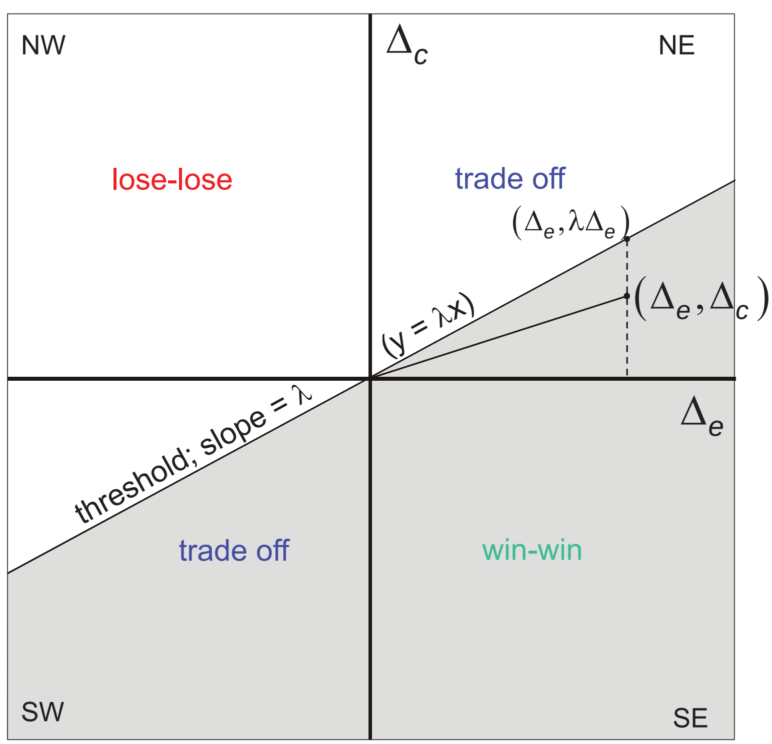
Model Definitions

T is considered cost-effective if, and only if, $\lambda\Delta_e > \Delta_c$

That is if, and only if $\lambda\Delta_e - \Delta_c > 0$

That is if, and only if, INB is greater than zero

Cost-effectiveness Plane



$\Delta_e\lambda < \Delta_c$, *i.e.* $b(\lambda) < 0$

$\Delta_e\lambda > \Delta_c$, *i.e.* $b(\lambda) > 0$

Model Definitions

T is cost-effective if, and only if $\lambda\Delta_e > \Delta_c$

i.e. iff $\lambda > \frac{\Delta_c}{\Delta_e} \equiv R \quad (\Delta_e > 0)$; or $\lambda < \frac{\Delta_c}{\Delta_e} \equiv R \quad (\Delta_e < 0)$

R is referred to as the incremental cost-effectiveness ratio (ICER)

T is cost-effective iff

(1) $b(\lambda) > 0$

OR

(2) $R < \lambda$ if $\Delta_e > 0$; or $R > \lambda$ if $\Delta_e < 0$

Model Definitions

Incremental cost-effectiveness ratio (ICER) = $R = \frac{\Delta_c}{\Delta_e} = \Delta_c \frac{1}{\Delta_e}$

= the additional cost per patient $\times$ NNT

= additional cost to realize an extra unit of effectiveness from using T rather than S

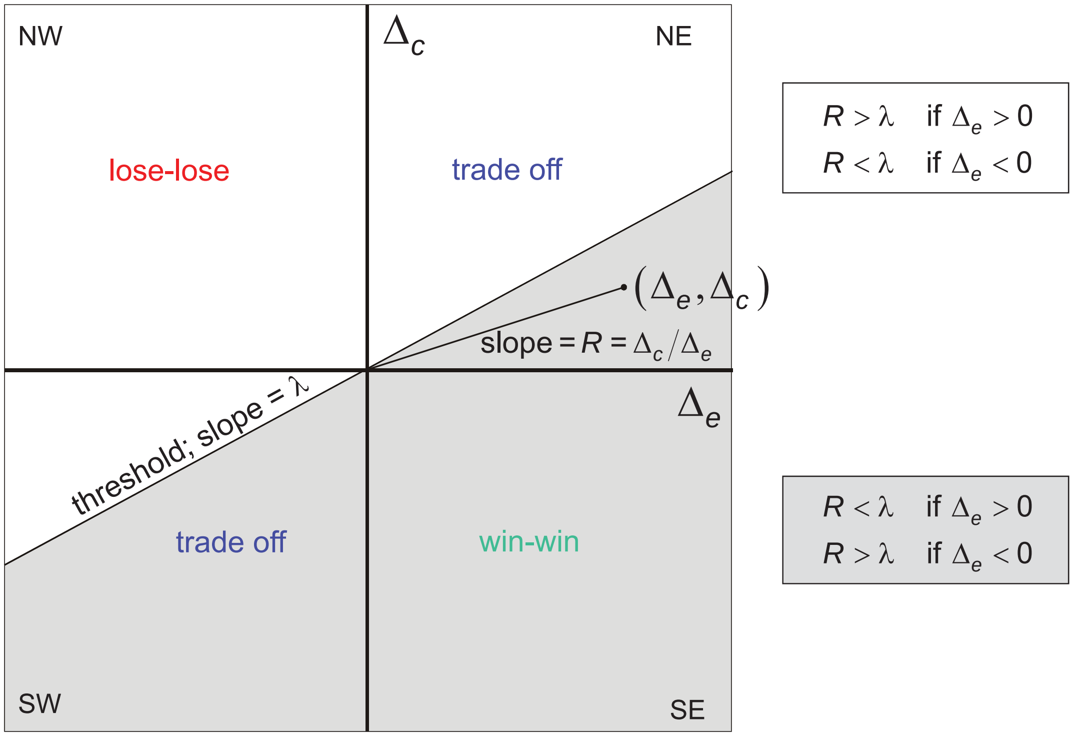
for survival: ICER = cost of saving a life

for survival time: ICER = cost of an additional year of life

for quality-adjusted survival time:

ICER = cost of an additional QALY

Cost-effectiveness Plane



Inference on Incremental Net Benefit

$H: b(\lambda) \leq 0$ versus $A: b(\lambda) > 0$

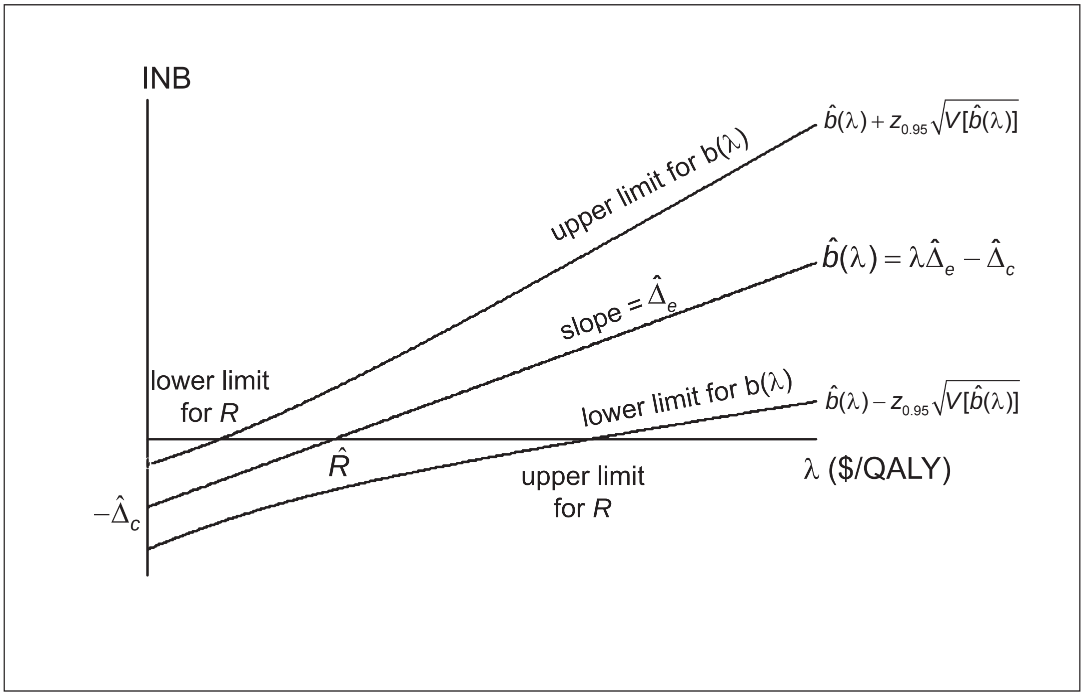
$\hat{b}(\lambda) = \lambda\hat{\Delta}_e - \hat{\Delta}_c$ and $V[\hat{b}(\lambda)] = \lambda^2 V(\hat{\Delta}_e) + V(\hat{\Delta}_c) - 2\lambda C(\hat{\Delta}_e, \hat{\Delta}_c)$

$Z = \hat{b}(\lambda) \big/ \sqrt{V[\hat{b}(\lambda)]}$ Reject H in favour of A if $Z > z_{0.95}$ (= 1.65),

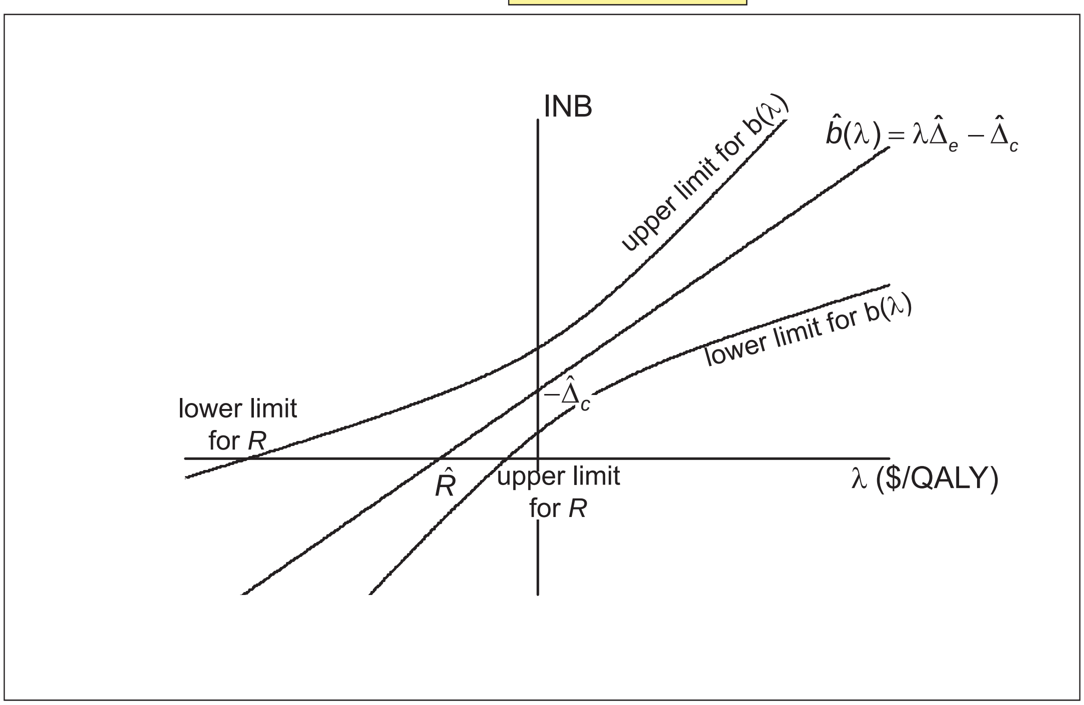
where $z_{0.95}$ is the 95th percentile of the standard normal random variable

90% confidence limits: $\hat{b}(\lambda) \pm z_{0.95}\sqrt{V[\hat{b}(\lambda)]}$

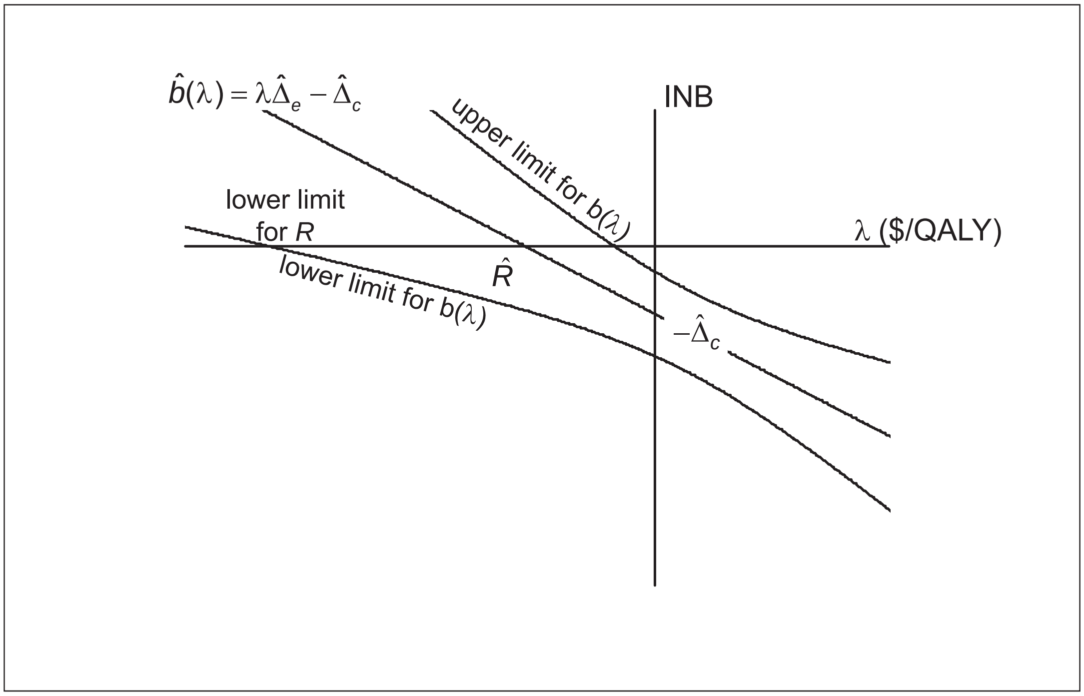
N-E Quadrant $\hat{\Delta}_e > 0, \quad \hat{\Delta}_c > 0$



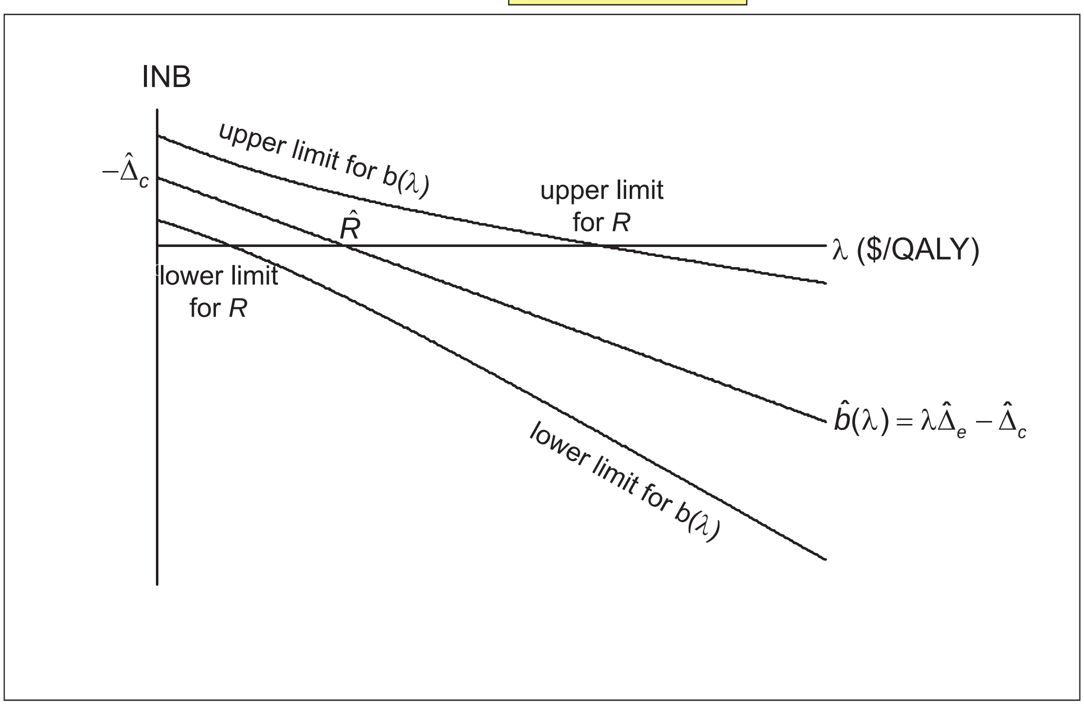
S-E Quadrant $\hat{\Delta}_e > 0, \quad \hat{\Delta}_c < 0$



N-W Quadrant $\hat{\Delta}_e < 0, \quad \hat{\Delta}_c > 0$



S-W Quadrant $\hat{\Delta}_e < 0, \quad \hat{\Delta}_c < 0$



Fieller Confidence Limits for the ICER

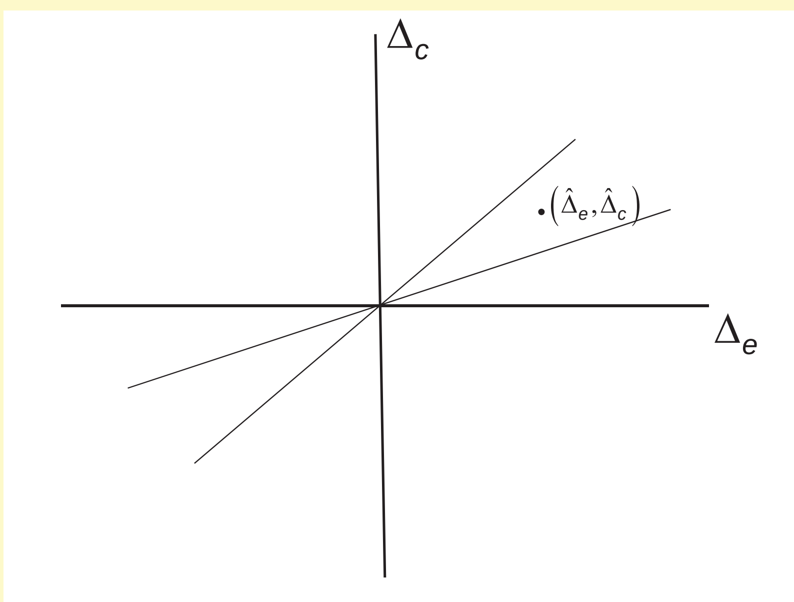
Estimate of the ICER = $\frac{\hat{\Delta}_c}{\hat{\Delta}_e} = \hat{R}$ is biased, but consistent

90% Fieller confidence limits for the ICER given by

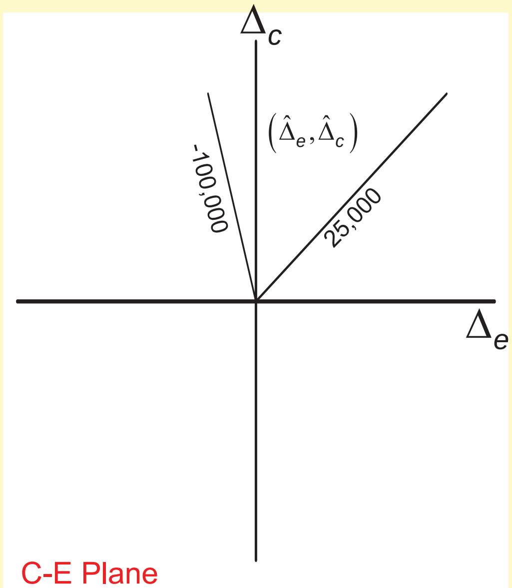
$$\hat{R}\left\{\left(1 - z_{0.95}^2 c \pm z_{0.95}\sqrt{a + b - 2c - z_{0.95}^2(ab - c^2)}\right) \Big/ \left(1 - z_{0.95}^2 a\right)\right\},\text{ where}$$

$$a = \frac{V(\hat{\Delta}_e)}{\hat{\Delta}_e^2},\ b = \frac{V(\hat{\Delta}_c)}{\hat{\Delta}_c^2},\ c = \frac{C(\hat{\Delta}_e, \hat{\Delta}_c)}{\hat{\Delta}_e \hat{\Delta}_c}$$

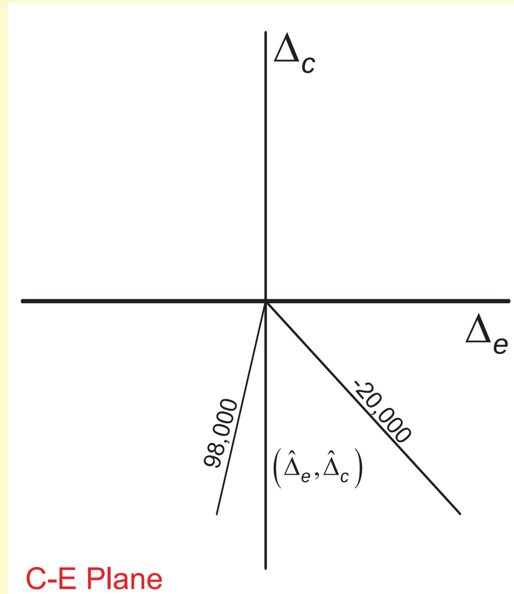
Fieller Limits as a Bowtie



Fieller limits, straddling the vertical axis

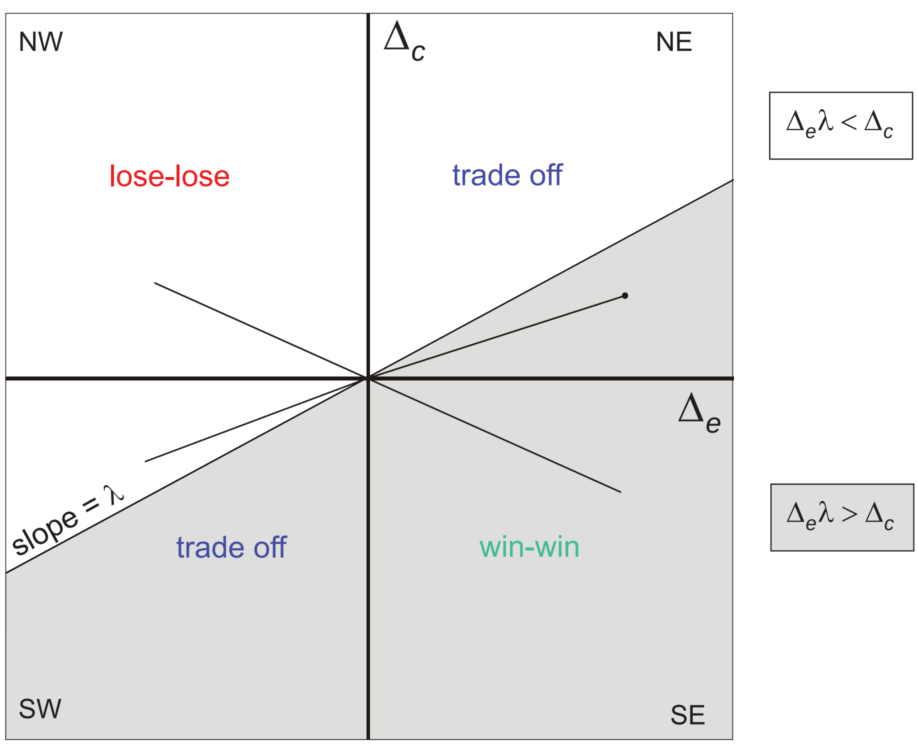


(A) Confidence interval 25,000 to $+\infty$ and $-\infty$ to -100,000



(B) Confidence interval 98,000 to $+\infty$ and $-\infty$ to -20,000

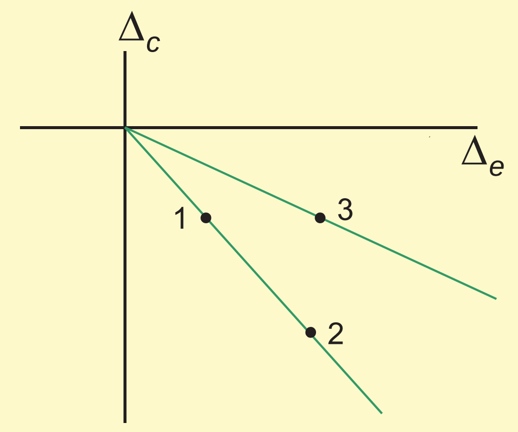
Problems with ICERs



Problems with ICERS

Not properly ordered in “win-win” and “lose-lose” quadrants

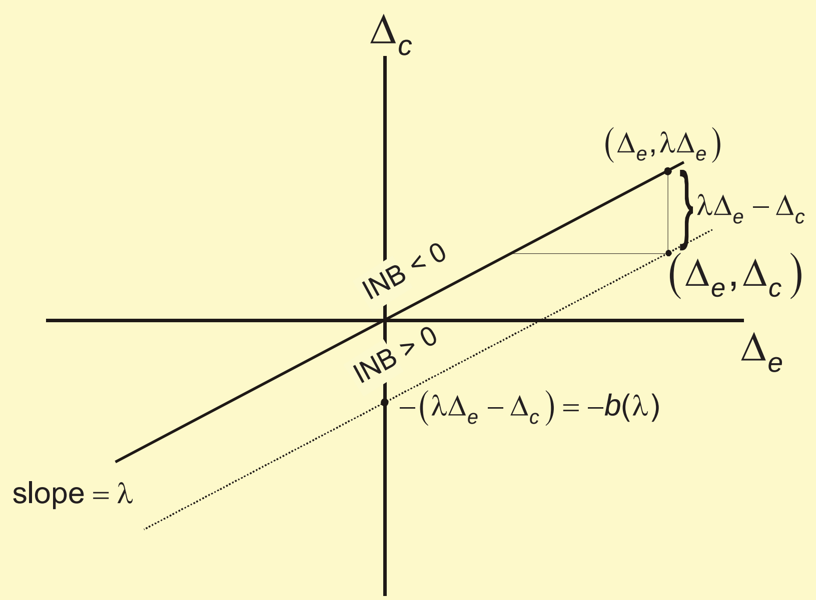
	Effect (yrs)	Cost ($)	
T1	5	8	
T2	7	6	
T3	7	8	
S	3	10	ICER
Δ1	2	-2	-1
Δ2	4	-4	-1
Δ3	4	-2	-0.5



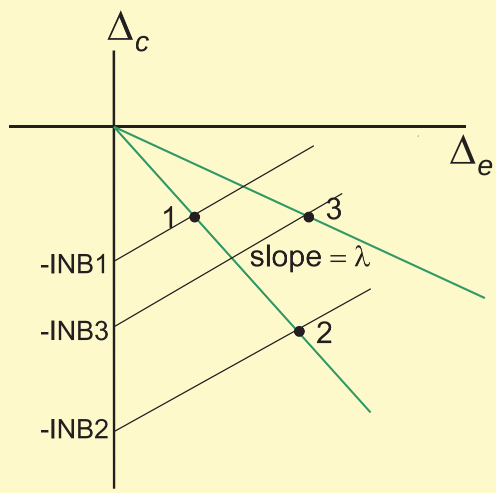
2 better than 3 better than 1

ICER2 = ICER1 < ICER3

Incremental Net Benefit on the C-E Plane



Problems with ICERS Solved by INB



2 better than 3 better than 1

INB2 > INB3 > INB1

Cost-effectiveness Acceptability Curves (CEAC)

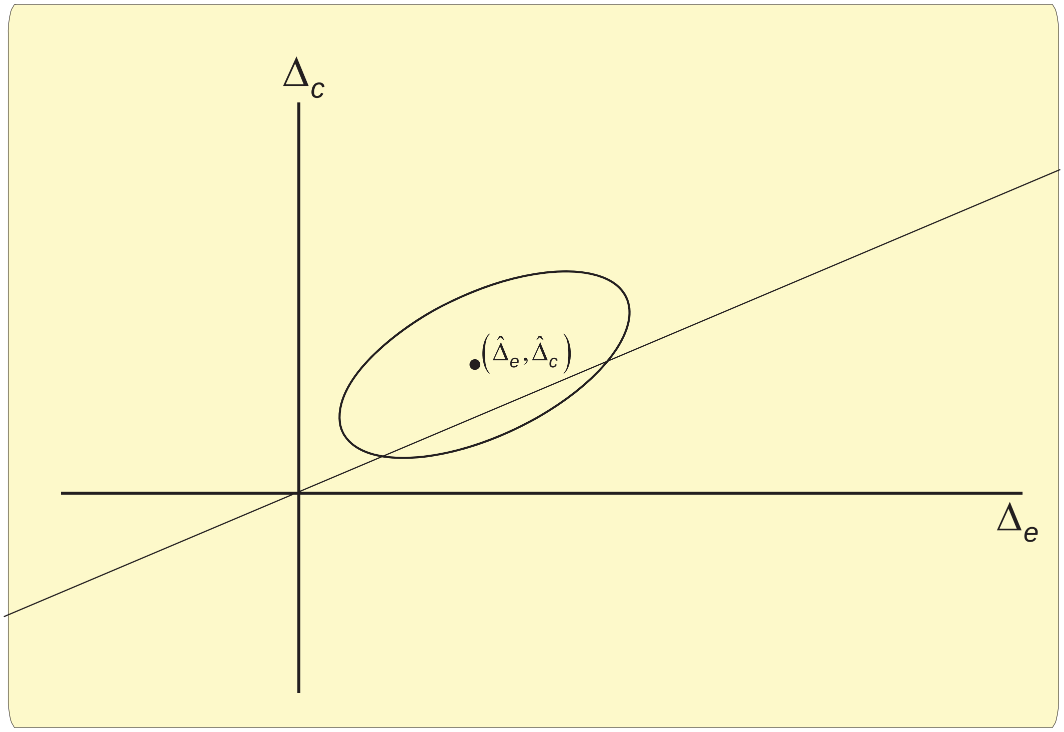
Plot of the probability that *T* is cost-effective
as a function of the threshold value for health outcome

That is, $\Pr(\lambda\Delta_e - \Delta_c > 0)$ as a function of λ; $\left(\mathcal{A}(\lambda)\right)$

Bayesian concept, but the CEAC is not a probability distribution

Can have negative slope

Cost-effectiveness Acceptability Curves (CEAC)



Cost-effectiveness Acceptability Curves

Can be given by $\text{CEAC}_\lambda = \Phi\left(\hat{b}(\lambda) \big/ \sqrt{V(\hat{b}(\lambda))}\right)$

Where $\Phi(\cdot)$ is the *cdf* for a standard normal random variable

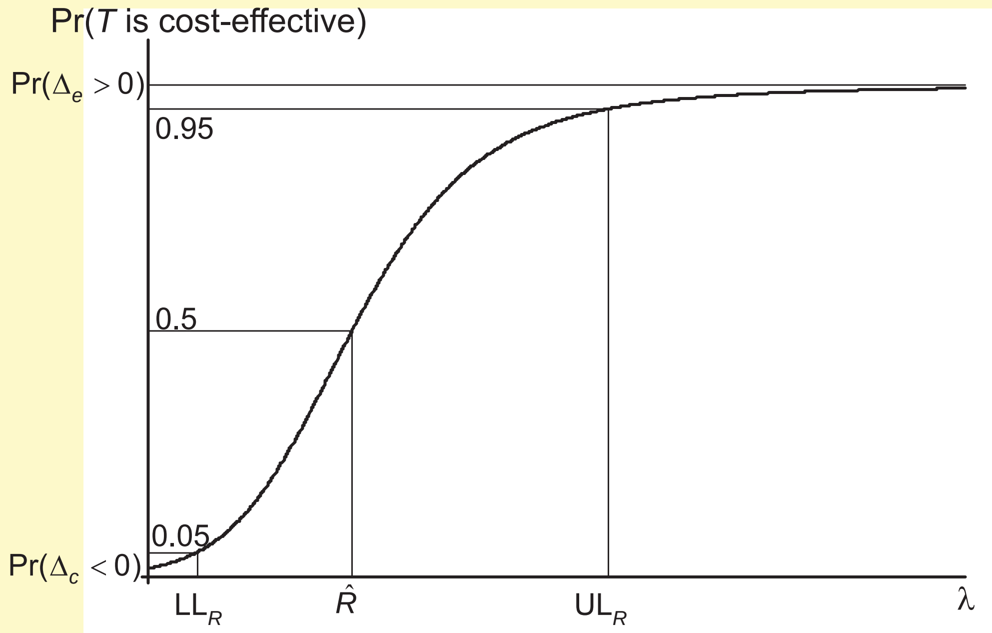
Assumes Δ_e and Δ_c are normally distributed and no prior information

$\text{CEAC}_{\lambda=0}$ = Prob($\Delta_c < 0$) *i.e.* Treatment is cost-saving

$\text{CEAC}_{\lambda=\infty}$ = Prob($\Delta_e > 0$) *i.e.* Treatment is effective

$\text{CEAC}_{\lambda=\text{conf. limits of ICER}}$ = 0.05 and/or 0.95

Cost-effectiveness Acceptability Curves



Parameter Estimation

Need to estimate $\Delta_e, \Delta_c, V(\hat{\Delta}_e), V(\hat{\Delta}_c), C(\hat{\Delta}_{e,}\hat{\Delta}_c)$

Estimation procedures depend on:

- whether or not skewed nature of cost data is accounted for
- whether or not covariates are adjust for
- whether or not random effects (clinical site or country) are accounted for
- whether or not the data are censored

skewed, covariates, random effects, censored = (N, N, N, N)

Mitoxantrone + Prednisone (*T*) versus Prednisone alone (*S*) for symptomatic hormone resistant prostate cancer

161 patients

No difference in survival

Better palliation with *T*

Cost data on 114 patients from the 3 largest centres

Retrospective chart review; included hospital admissions, outpatient visits, investigations, therapies and palliative care

Quality-adjusted survival using EORTC QLQ-C30

Prostate Cancer Example

Let e_{ji} and c_{ji} be the observed effectiveness and cost,

respectively for patient *i* on arm $j = T,S$

Let $\hat{e}_j$ and $\hat{c}_j$ be the averages (over *i*)

Then $\hat{\Delta}_e = \hat{e}_T - \hat{e}_S$ and $\hat{\Delta}_c = \hat{c}_T - \hat{c}_S$

Prostate Cancer Example

Unpooled	Pooled
$\hat{V}(\hat{\Delta}_e) = \hat{V}(\hat{e}_T) + \hat{V}(\hat{e}_S) = \sum_{j=T}^{S}\sum_{i=1}^{n_j}\frac{(e_{ji}-\hat{e}_j)^2}{n_j(n_j-1)}$	$\left(\frac{n_T+n_S}{n_T n_S}\right)\frac{\sum_{j=T}^{S}\sum_{i=1}^{n_j}(e_{ji}-\hat{e}_j)^2}{n_T+n_S-2}$
$\hat{V}(\hat{\Delta}_c) = \hat{V}(\hat{c}_T) + \hat{V}(\hat{c}_S) = \sum_{j=T}^{S}\sum_{i=1}^{n_j}\frac{(c_{ji}-\hat{c}_j)^2}{n_j(n_j-1)}$	$\left(\frac{n_T+n_S}{n_T n_S}\right)\frac{\sum_{j=T}^{S}\sum_{i=1}^{n_j}(c_{ji}-\hat{c}_j)^2}{n_T+n_S-2}$
$\hat{C}(\hat{\Delta}_e,\hat{\Delta}_c) = \hat{C}(\hat{e}_T,\hat{c}_T) + \hat{C}(\hat{e}_S,\hat{c}_S) = \sum_{j=T}^{S}\sum_{i=1}^{n_j}\frac{(e_{ji}-\hat{e}_j)(c_{ji}-\hat{c}_j)}{n_j(n_j-1)}$	$\left(\frac{n_T+n_S}{n_T n_S}\right)\frac{\sum_{j=T}^{S}\sum_{i=1}^{n_j}(e_{ji}-\hat{e}_j)(c_{ji}-\hat{c}_j)}{n_T+n_S-2}$

Prostate Cancer Example

	Treatment	Standard	
$\hat{e}_j$	40.9	28.1	difference = $\hat{\Delta}_e$ = 12.8
$\hat{V}(\hat{e}_j)$	24.1	16.4	sum = $\hat{V}(\hat{\Delta}_e)$ = 40.5
$\hat{c}_j$	27,322	29,039	difference = $\hat{\Delta}_c$ = -1717
$\hat{V}(\hat{c}_j)$	6,466,351	7,872,681	sum = $\hat{V}(\hat{\Delta}_c)$ = 14,339,032
$\hat{C}(\hat{e}_j,\hat{c}_j)$	2771	2876	sum = $\hat{C}(\hat{\Delta}_e,\hat{\Delta}_c)$ = 5647

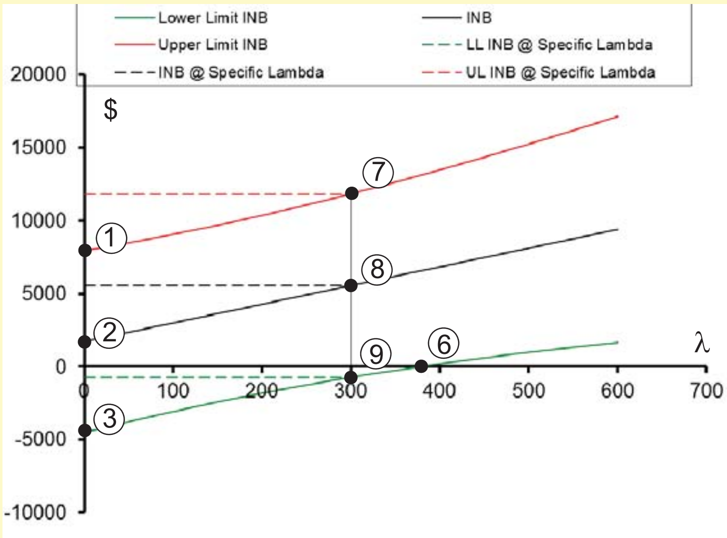
ICER = -1717/12.8 = -134.14

$$\hat{b}(\lambda) = \hat{\Delta}_e\lambda - \hat{\Delta}_c = 12.8\lambda + 1717$$

$$\hat{V}[\hat{b}(\lambda)] = \hat{V}(\hat{\Delta}_e)\lambda^2 + \hat{V}(\hat{\Delta}_c) - 2\hat{C}(\hat{\Delta}_e,\hat{\Delta}_c)\lambda$$
$$= 40.5\lambda^2 + 14339032 - 11294\lambda$$

90% confidence interval

$$= \hat{b}(\lambda) \pm z_{0.95}\sqrt{\hat{V}[\hat{b}(\lambda)]}$$
$$= \hat{b}(\lambda) \pm 1.65\sqrt{\hat{V}[\hat{b}(\lambda)]}$$



$$2 = (0, -\hat{\Delta}_c) = (0, 1717)$$

$$1 = (0, UL_{-\Delta_c}) = (0, -LL_{\Delta_c}) = (0, 7949)$$

$$3 = (0, LL_{-\Delta_c}) = (0, -LL_{\Delta_c}) = (0, -4467)$$

$$5 = (\hat{R}, 0) = (-134, 0)$$

$$4 = (LL_R, 0) = (-1765, 0)$$

$$6 = (UL_R, 0) = (378, 0)$$

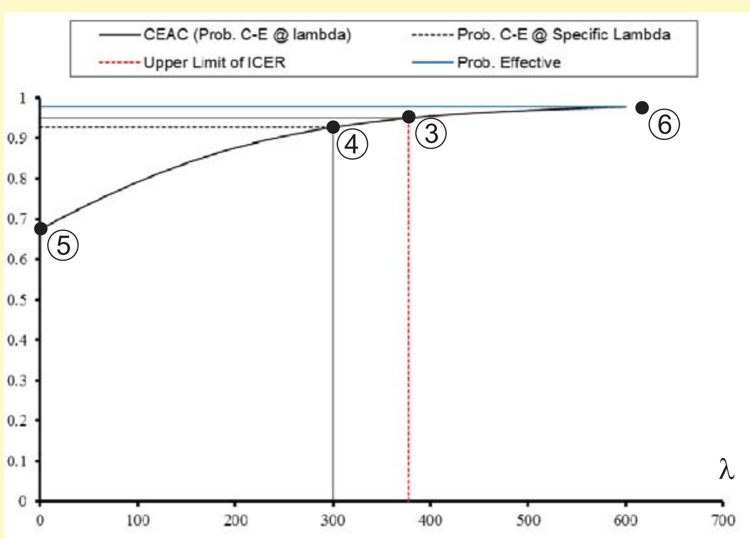
$$8 = (300, \hat{b}(300)) = (300, 5557)$$

$$7 = (300, UL_{b(300)}) = (300, 11841)$$

$$9 = (300, LL_{b(300)}) = (300, -727)$$

$$z = \frac{\hat{b}(300)}{\hat{V}\left(\hat{b}(300)\right)} = \frac{5557}{3820} = 1.46$$

Cost-effectiveness Acceptability Curve



$$1 = (LL_R, 0.05) = (-1750, 0.05)$$

$$2 = (\hat{R}, 0.5) = (-134, 0.5)$$

$$3 = (UL_R, 0.95) = (376, 0.95)$$

$$4 = \left(300, \Pr(b(300) > 0)\right) = (300, 0.93)$$

$$5 = \left(0, \Pr(\Delta_c < 0)\right) = (0, 0.67)$$

$$6 = ("\infty", \Pr(\Delta_e > 0) = ("\infty", 0.98)$$

The ASsessment of the Safety and Efficacy of New Thrombolytic Regimens (ASSENT)-3 trial

6095 patients from 575 sites in 26 countries

with ST-elevated AMI randomized to 3 arms

- Heparin: full-dose tenecteplase + unfractionated heparin
- Enoxaparin: full-dose tenecteplase + enoxaparin
- Abciximab: half-dose tenecteplase + unfractionated heparin + abciximab

(duration of interest = 30 days)

Composite measure of effectiveness:

Freedom from (i) death, (ii) re-infarction and (iii) refractory ischemia

ASSENT-3 trial

Let e_{ji} = 1 if patient i on arm j has a success, 0 otherwise

Then $\hat{e}_j$ = proportion of success on arm j

As before $\hat{\Delta}_e = \hat{e}_T - \hat{e}_S$

$$\hat{V}\left(\hat{\Delta}_e\right) = \frac{\hat{e}_T(1-\hat{e}_T)}{n_T} + \frac{\hat{e}_S(1-\hat{e}_S)}{n_S}$$

$$C\left(\hat{\Delta}_e, \hat{\Delta}_c\right) = \frac{\left(c_{T\{1\}} - n_T\hat{e}_T\hat{c}_T\right)}{n_T(n_T-1)} + \frac{\left(c_{S\{1\}} - n_S\hat{e}_S\hat{c}_S\right)}{n_S(n_S-1)},$$

where $c_{j\{1\}} = \sum_{i=1}^{n_j} e_{ji}c_{ji}$ = sum of cost for patients with success

ASSENT-3 Trial

Abciximab (T) vs Heparin (S)

$$\hat{\Delta}_e = 0.0373 \qquad \hat{V}\left(\hat{\Delta}_e\right) = 0.0001124$$

$$\hat{\Delta}_c = 949 \qquad \hat{V}\left(\hat{\Delta}_c\right) = 23375$$

$$\hat{C}\left(\hat{\Delta}_e, \hat{\Delta}_c\right) = -0.4410$$

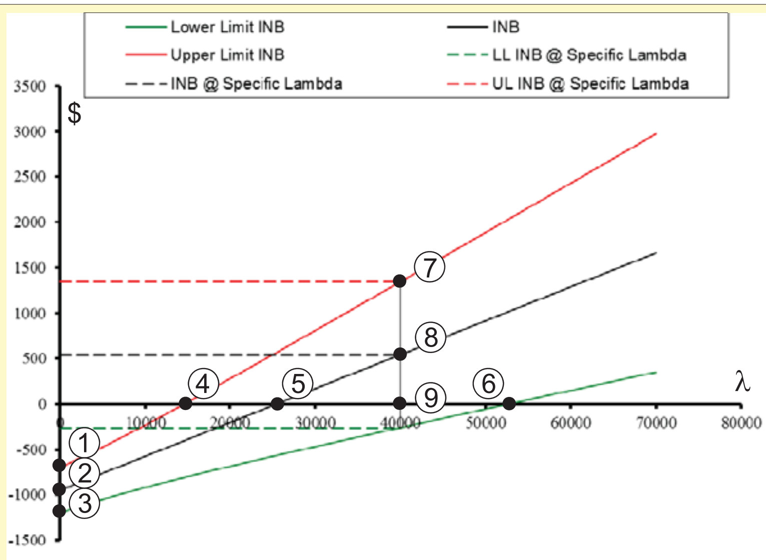
ICER = 949/0.0373 = 25442

$$\hat{b}(\lambda) = \hat{\Delta}_e \lambda - \hat{\Delta}_c = 0.0373\lambda - 949$$

$$V[\hat{b}(\lambda)] = \hat{V}(\hat{\Delta}_e)\lambda^2 + \hat{V}(\hat{\Delta}_c) - 2\hat{C}(\hat{\Delta}_e, \hat{\Delta}_c)\lambda$$
$$= 0.0001124\lambda^2 + 23375 + 0.882\lambda$$

90% confidence interval

$$= \hat{b}(\lambda) \pm z_{0.95}\sqrt{\hat{V}[\hat{b}(\lambda)]}$$
$$= \hat{b}(\lambda) \pm 1.65\sqrt{\hat{V}[\hat{b}(\lambda)]}$$



Abciximab (T) vs Heparin (S)

$$2 = (0, -\hat{\Delta}_c) = (0, -949)$$

$$1 = (0, UL_{-\Delta_c}) = (0, -LL_{\Delta_c}) = (0, -698)$$

$$3 = (0, LL_{-\Delta_c}) = (0, -LL_{\Delta_c}) = (0, -1200)$$

$$5 = (\hat{R}, 0) = (25442, 0)$$

$$4 = (LL_R, 0) = (14616, 0)$$

$$6 = (UL_R, 0) = (52697, 0)$$

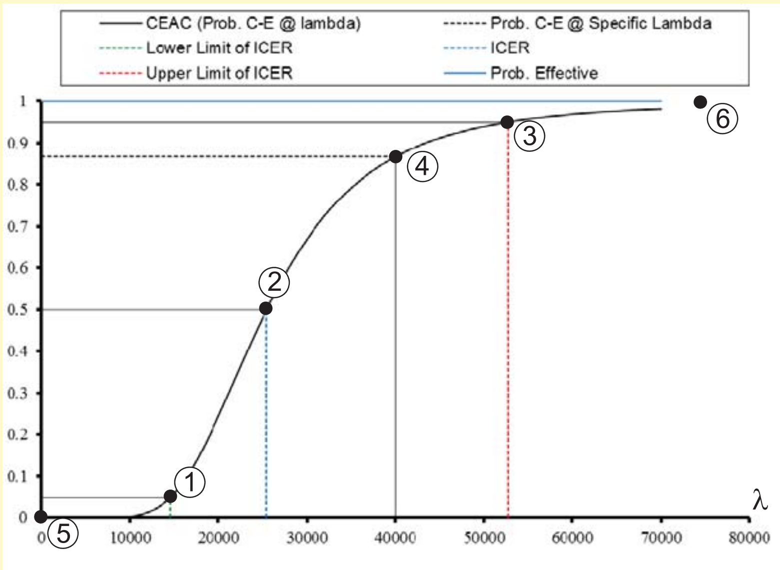
$$8 = (40000, \hat{b}(40000)) = (40000, 543)$$

$$7 = (40000, UL_{b(40000)}) = (40000, 1349)$$

$$9 = (40000, LL_{b(40000)}) = (40000, -259)$$

$$z = \frac{\hat{b}(40000)}{\hat{V}\left(\hat{b}(40000)\right)} = \frac{543.0}{488.4} = 1.11$$

Cost-effectiveness Acceptability Curve



Abciximab (*T*) vs Heparin (*S*)

$1 = (LL_R, 0.05)$
$= (14616, 0.05)$

$2 = (\hat{R}, 0.5)$
$= (25442, 0.5)$

$3 = (UL_R, 0.95)$
$= (52687, 0.95)$

$4 = (40000, \Pr(b(40000) > 0))$
$= (40000, 0.87)$

$5 = (0, \Pr(\Delta_c < 0)) = (0, 0.27 \times 10^{-9})$
$6 = (\text{"}\infty\text{"}, \Pr(\Delta_e > 0) = (\text{"}\infty\text{"}, 0.9998)$

skewed, covariates, random effects, censored = (Y, N, N, N)

Mitoxantrone + Prednisone (*T*) versus Prednisone alone (*S*) for symptomatic hormone resistant prostate cancer

I tend to use a gamma distribution for costs,

facilitated by the procedure GENMOD in SAS.

SAS Code

```
*comment: estimate Δe and its variance
          treatment = 1 for T and treatment = 0 for S
          dist=bin for binary measure for effectiveness;
proc genmod data=dataset desc;
          model qalw = treatment / dist=normal link=identity;
          output out=e predicted=pred_e;
run;

*comment: estimate Δc and its variance;
proc genmod data= dataset desc;
          model cost = treatment / dist=gamma link=identity;
          output out=c predicted=pred_c;
run;

*comment: estimate correlation between Δe and Δc to provide variance;
data temp; merge e c; resid_e = qalw - pred_e; resid_c = cost - pred_c; run;
proc corr data=temp nosimple; var resid_e resid_c; run;
```

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	28.1113	4.6999	18.8998	37.3229	35.78	<.0001
TRT	1	12.7805	6.4250	0.1877	25.3732	3.96	0.0467

$\hat{\Delta}_e = 12.78; \quad V\left(\hat{\Delta}_e\right) = (6.4250)^2$

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	29038.86	2586.838	23968.75	34108.97	126.01	<.0001
TRT	1	-1717.08	3440.727	-8460.78	5026.620	0.25	0.6177

$\hat{\Delta}_c = -1717.08; \quad V\left(\hat{\Delta}_c\right) = (3440.727)^2$

Pearson Correlation Coefficients, N = 114

	resid_e	resid_c
resid_e	1.00000	0.23224 0.0129
resid_c	0.23224 0.0129	1.00000

$Cov\left(\hat{\Delta}_e, \hat{\Delta}_c\right) = 0.23224 * 6.4250 * 3440.727$

Prostate Example

Assuming gamma (normal) distribution for costs

$\hat{\Delta}_e = 12.8$ (12.8)

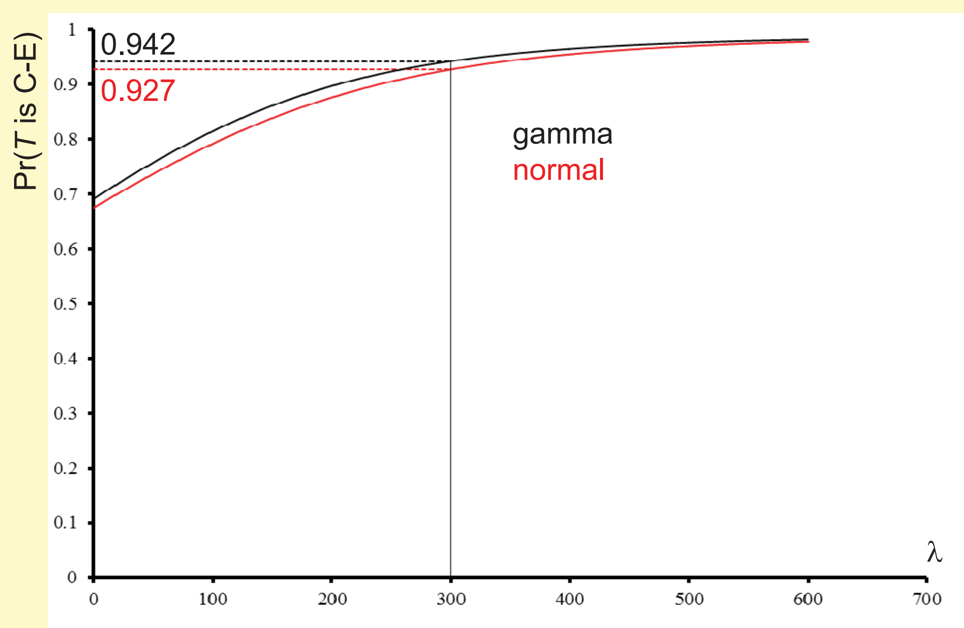
$\hat{V}(\hat{\Delta}_e) = 41.3$ (40.5)

$\hat{\Delta}_c =$ -1717 (-1717)

$\hat{V}(\hat{\Delta}_c) = 11{,}838{,}602$ (14,339,032)

$\hat{C}(\hat{\Delta}_e, \hat{\Delta}_c) = 5134$ (5647)

CEACs for Prostate Example



Summary I

Need to estimate 5 parameters: $\Delta_e, \Delta_c, V(\hat{\Delta}_e), V(\hat{\Delta}_c), C(\hat{\Delta}_e, \hat{\Delta}_c)$

Estimation procedures depend on:

- whether or not skewed nature of cost data is accounted for
- whether or not covariates are adjust for
- whether or not random effects (clinical site or country) are accounted for
- whether or not the data are censored

Summary II

If skewing is ignored, and there are no covariates or random effects, and the data are not censored, then parameter estimation is simply Stats 101.

For other situations see:
Willan and Briggs (2006) *The Statistical Analysis of Cost-effectiveness Data*. Wiley & Sons, Chichester.

Summary III

With parameter estimates one can calculate:

- ICER and confidence limits
- INB and confidence limits
- Cost-effectiveness acceptability curve

Tutorial

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Day 2 1030-1200.xlsx